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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/422,999	10/22/1999	HIROAKI KAWASAKI	MIT-103	6219
21323	7590	12/18/2003	EXAMINER	
TESTA, HURWITZ & THIBEAULT, LLP			MURPHY, JOSEPH F	
HIGH STREET TOWER				
125 HIGH STREET			ART UNIT	PAPER NUMBER
BOSTON, MA 02110			1646	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 09/422,999	Applicant(s) KAWASAKI ET AL.
	Examiner	Art Unit
	Joseph F Murphy	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### **Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## **Status**

1)  Responsive to communication(s) filed on 22 September 2003.

2a)  This action is **FINAL**.                            2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

4)  Claim(s) 40-47, 50-54, 62 and 131-134 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 40-47, 50-54, 62, 131-134 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are: a)  accepted or b)  objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)  The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All b)  Some \* c)  None of:  
1.  Certified copies of the priority documents have been received.  
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

13)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a)  The translation of the foreign language provisional application has been received.

14)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1)  Notice of References Cited (PTO-892) 4)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_ .  
2)  Notice of Draftsperson's Patent Drawing Review (PTO-948) 5)  Notice of Informal Patent Application (PTO-152)  
3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6)  Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Formal Matters***

Claims 40-47, 50-54, 62, 131-134 are pending and under consideration.

### ***Response to Amendment***

Applicant's arguments filed 9/22/2003 have been fully considered.

The objection to claim 62 has been obviated by Applicant's amendment and is thus withdrawn.

The rejection of claims 42, 51 and 54 has been obviated by Applicant's amendment and is thus withdrawn.

Remaining issues, and new issues, are set forth below.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 50, 52, 131, 132 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims as written read on embryonic stem cells, gametes and germ line cells transfected with a nucleic acid. As it would be possible that these cells could be used in a process of in vitro fertilization and implantation, they read on a transgenic human, which is not patentable subject matter.

***Claim Rejections - 35 USC § 112 first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-47, 50-54, 62, 131-134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a full length nucleic acid of SEQ ID NO: 17, does not reasonably provide enablement for a nucleic acid which is complementary to SEQ ID NO: 17, nor host cells comprising these nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass nucleic acids that are complementary to SEQ ID NO: 17. There are no length or homology limitations, nor any functional limitations set forth for these claims. Claims 40-47, 50-54, 62, 131-134 are overly broad since insufficient guidance is provided as to which of the myriad of variant polynucleotides will retain the characteristics of cAMP-GEF. The claims are thus directed to nucleic acids which encode variant polypeptides. However, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of cAMP-GEF. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF,

including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a functional limitation for the encoded variant polypeptides, and since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for

functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass nucleic acids encoding polypeptides that the specification only teaches one skilled in the art to test for functional variants. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polynucleotides, and since detailed information regarding the structural and functional requirements of the encoded polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for nucleic acids encoding polypeptide variants of cAMP-GEF, and has not taught how to make nucleic acids encoding polypeptide variants of cAMP-GEF, it would require undue experimentation of one of skill in the art to make and use the claimed polynucleotides.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claims 50, 52, 131, 132 as they read on the use embryonic stem cells for the creation of transgenic non-human animals:

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a nucleic acid other than a transgenic animal comprising a nucleotide sequence set forth in SEQ ID NO: 17. It is well known in the art that the production of transgenic animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only “putative” ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seemark (Reproductive Fertility and Development, 1994) supports this

observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that “although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated.” (page S38, column 1, first paragraph). As the claims encompass transgenic non-human animals, which must be generated by the introduction of a transgene into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic non-human animals of species other than the mouse.

Claims 40-47, 50-54, 62, 131-134 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are directed to nucleic acids that are complementary to SEQ ID NO: 17. There are no length or homology limitations, nor any functional limitations set forth for these claims. The claims are thus directed to nucleic acids encoding variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared

by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the cAMP-GEF variants. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 17 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that

could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

*Conclusion*

No claim is allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Joseph F. Murphy, Ph. D.  
Patent Examiner  
Art Unit 1646  
December 2, 2003